REMARKS

In the aforementioned action, the examiner rejects claims 1-5, 8 and 9 as allegedly obvious over Leippe or Andra, and further in view of Pinto *et al.*, Rivett *et al.*, and Liu *et al.* Specifically, the examiner asserts that "[t]he state of the art is such that making the product (amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine) is accomplished with a reasonable expectation of success" (office action at 6). Thus, it appears that the examiner is drawing an analogy between the small molecule drugs taught in Pinto and the lytic peptides of the present invention.

While applicants' arguments to the instant rejection were set forth in an August 18th response, applicants wish to add the following comments regarding the Pinto reference:

Pinto describe the use of poly-γ-glutamates to devise a folate prodrug and prevent cell entry, while the instant invention teaches the use of γ-glutamates to inhibit peptide folding by charge neutralization. These are two completely distinct and unrelated concepts for devising compositions for treatment that comprise γ-glutamates.

In particular, Pinto *et al.* teach glutamation and deglutamation of methotrexate (MTX) to facilitate entry **into a cell**. The reference states that

> PSMA sequentially removes poly-gamma glutamates from dietary folates, which are then able to be transported into the cell. Folate derivatives, as well as analogs and antagonists that are poly-γ-glutamated do not readily traverse plasma membranes unless they are deglutamated. Conversely, once deglutamated and transported into cells, folate derivatives are readily glutamated and thus are retained intracellularly."

Pinto at 22, first full paragraph. As such, glutamated folates and analogs thereof will not readily traverse a plasma membrane, but deglutamated folates such as MTX will cross the cell membrane and accumulate inside a cell, where it inhibits dihydrofolate reductase. The significance of PSMA in Pinto is therefore apparent. Pinto identifies PSMA as a folate hydrolase (Pinto *et al.*, *Clin. Cancer Res.*, 2:1445-1451 (1996)), and uses PSMA to deglutamate $MTXglu_3$ and facilitate MTX entry.

This is in sharp contrast with the present invention, which (1) describes the use of poly-γ-glutamates **in charge neutralization** to inhibit proper peptide folding, and (2) discloses compositions that **do not act intracellularly** to cause cell toxicity. Thus, one of skill in the art, based on the teachings of Pinto, would not add gamma glutamate residues to a lytic peptide so as to prevent formation of a cytotoxic conformation. Clearly, **Pinto does not teach adding poly-γ-glutamates for peptide inactivation on the basis of charge neutralization**.

Furthermore, Pinto describe that "clinical trials have not displayed appreciable activity with MTX as a single agent in the treatment of human prostate cancer" (Pinto at 22, first full paragraph). Accordingly, the Pinto reference relates to overcoming this barrier and teaching the value of MTX in prostate cancer treatment. As previously stated, Pinto take advantage of the "importance of [the] glutamation/deglutamation process for the transport and activation of folate antagonists[,] and appreciat[e] the restricted overexpression of PSMA on prostate cancer cells" (Pinto at 22, first full paragraph). Pinto also state that "[t]he development of future therapeutic strategies in the treatment of prostate cancer should consider PSM-folate hydrolase as a target for prodrug activation using **folate antagonists or other chemotherapeutic agents** exhibiting a poly-γ-glutamated side chain" (Pinto at 23, last paragraph, emphasis added). As such, nowhere in Pinto is charge neutralization of peptides via glutamation taught, or even suggested.

In light of the foregoing, applicants respectfully assert that Pinto is unrelated to the present invention and in no way renders the claimed invention obvious.

CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments.

It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 12 Sept 2003

By _____

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No.19-0741for any such fees; and applicant(s) hereby petition for any needed extension of time.